

Polyunsaturated fatty acids and suicide risk in mood disorders: A systematic review

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ABSTRACT

Deficiency of omega-3 polyunsaturated fatty acids (PUFAs) and an alteration between the ratio of omega-3 and omega-6 PUFAs may contribute to the pathogenesis of bipolar disorder and unipolar depression. Recent epidemiological studies have also demonstrated an association between the depletion of fatty acid and suicide. Our aim was to investigate the relationship between PUFAs and suicide; assess whether the depletion of PUFAs may be considered a risk factor for suicidal behavior; in addition to detailing the potential use of PUFAs in clinical practice. We performed a systematic review on PUFAs and suicide in mood disorders, searching MedLine, Excerpta Medica, PsycLit, PsycInfo, and Index Medicus for relevant epidemiological, post-mortem, and clinical studies from January 1997 to September 2016. A total of 20 articles from peer-reviewed journals were identified and selected for this review. The reviewed studies suggest that subjects with psychiatric conditions have a depletion of omega-3 PUFAs compared to control groups. This fatty acid depletion has also been found to contribute to suicidal thoughts and behavior in some cases. However, large epidemiological studies have not supported this finding, as the depletion of omega-3 PUFAs was not detectable in all patients diagnosed with a mental illness and/or who engaged in suicidal behavior. Increasing PUFA intake may be relevant in the treatment of depression, however in respect to the prevention of suicide, the data is currently not supportive of this approach. Changes of levels of PUFAs may however be a risk factor to evaluate when assessing for suicide risk. Clinical studies should be conducted to prospectively assess whether prescriptive long-term use of PUFAs in PUFA-deficient people which depression may have a preventative role in attenuating suicide.

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1. Introduction

Omega-3 (n-3) and omega-6 (n-6) fatty acids may be considered in the group of polyunsaturated fatty acids (PUFAs) because their chain consists of several double bonds. The human body synthesizes omega-3 fatty acids from α -linolenic acid (De Gomez and Brenner, 1975) and this is possible through the competitive presence of omega-6 fatty acids, crucial chemical analogues derived by linoleic acid (De Gomez and Brenner, 1975; Hange and Christofferson, 1984). Food is the essential source of both the omega-3 α -linolenic acid and omega-6 linoleic acid as short chain fatty acids may be not converted into long chain fatty acids by humans, and therefore the tissue composition of n-3 PUFAs are crucially related to dietary consumption (Arterburn et al., 2006). n-3 and n-6 serum levels can be influenced by single nucleotide polymorphisms (SNPs) in fatty acid desaturase (FADS) genes which are partially involved in metabolic inter-conversion (Kiecolt-Glaser et al., 2010). Certain SNPs are potential modifying factors of the pharmacological treatment of psychiatric conditions (Evans et al., 2012), however it is relatively unknown as

to which SNPs may be implicated in modifying the pharmacokinetics and pharmacodynamics of PUFAs.

Omega-6 fatty acids may be considered a family of polyunsaturated fatty acids, having vegetable origin as well as the first carbon-carbon double bond in the n-6 position. The most important fatty acids within the omega-6 group are represented by: linoleic acid (18:2), an essential fatty acid, and the arachidonic acid (20:4), which is a precursor of prostaglandins (see Fig. 1). The competitive relationship with omega-3 fatty acids seems to modulate the potential pro-inflammatory effect of the omega-6 fatty acids. However, the most studied PUFAs are the omega-3 fatty acids. The omega-3 fatty acids share a carbon-carbon double bond in the n-3 position. The most important fatty acids within the omega-3 group are listed as follow: α -linolenic acid or ω 3 α (18:3; ALA), eicosapentaenoic acid (20:5, EPA), and docosahexaenoic acid (22:6, DHA) (see Fig. 1).

Various chronic psychiatric diseases report an imbalance in terms of omega-6/omega-3 ratio (Simopoulos, 2008). The omega-3 oils are involved in transmitting signals, moods and emotions (Lakhan and Viera, 2008); and levels are very low for instance in most bipolar patients (Osher et al., 2005). Research suggested that omega-3 fatty acid depletion can be involved in the pathogenesis of both bipolar disorder (BD) and major depressive disorder (MDD) (Freeman et al., 2006; Hibbeln, 1998; Noaghiul and Hibbeln, 2003; Peet, 2004). Patients with MDD have shown a significant decrease in red blood cell

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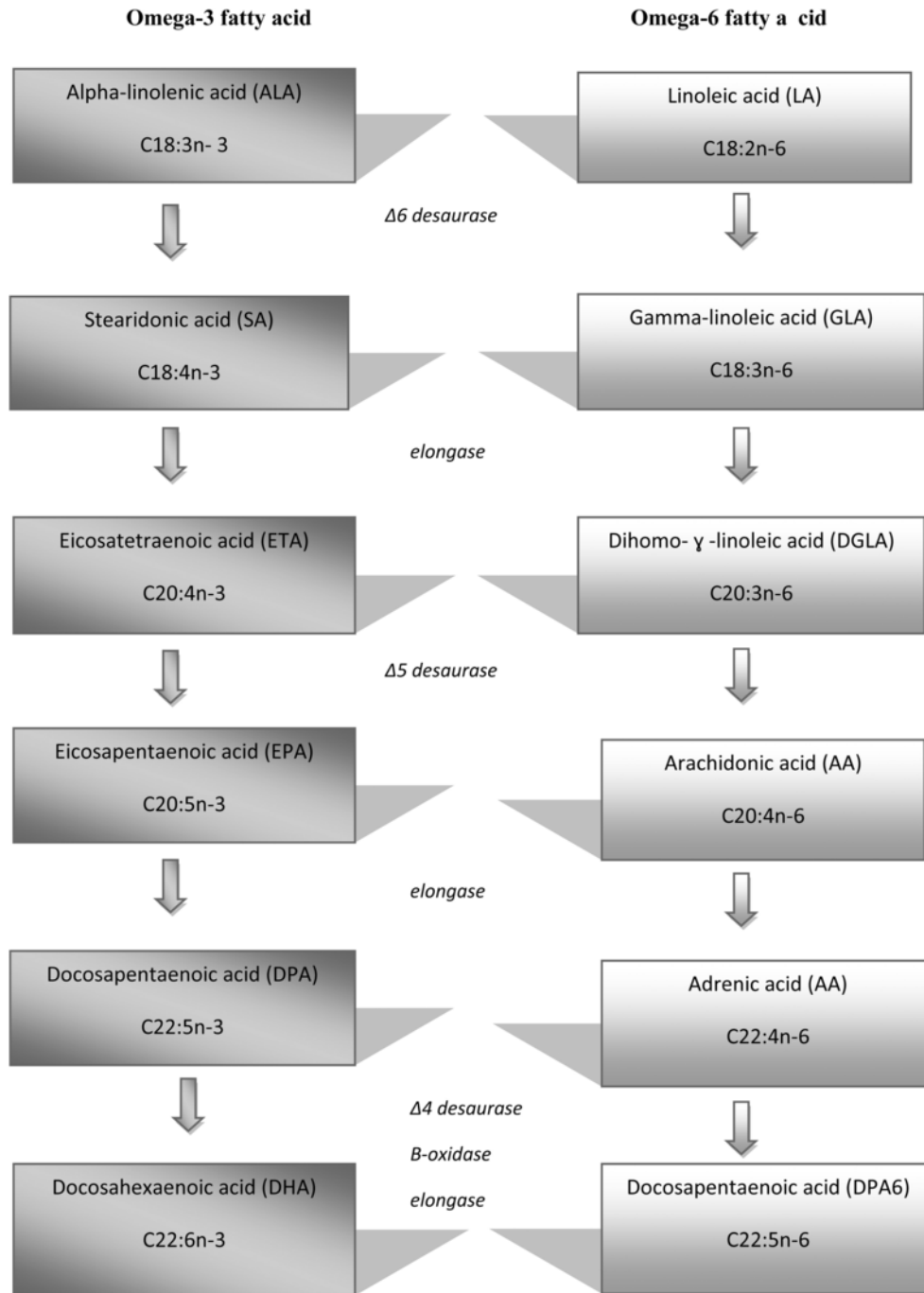


Fig. 1. Biosynthesis and metabolism of the principal polyunsaturated fatty acids.

(RBC) membrane DHA composition (Edwards et al., 1998; Peet et al., 1998) together with specific deficits in DHA composition of the orbitofrontal cortex according to post-mortem studies (McNamara et al., 2007a). Significant reductions have also been reported in RBC DHA and arachidonic acid composition among patients with BD (Chiu et al., 2003); however, the fatty acid composition of post-mortem brain tissue is poorly understood.

High fish consumption is associated with a reduced occurrence of psychiatric disorders (such as MDD and BD) and of psychopathological symptoms (impulsivity and aggression) and this decreased occurrence has in part been associated with omega-3 fatty acid levels

(Bozzatello et al., 2016; Hibbeln, 2009; Reis and Hibbeln, 2006). The current knowledge on DHA/EPA for brain function does not generate a rational daily intake recommendation, therefore the existing recommendations for cardiovascular protection could be taken as a minimum for brain protection (Parris, 2007). The American Heart Association recommends a minimum intake of two fish meals weekly for primary cardiovascular protection and 1000 mg/day of DHA/EPA for protection against a second heart attack (Parris, 2007). In Europe, different studies (one Norwegian and one German) recommend to take approximately one or two grams of DHA/EPA in healthy subjects (Eritsland, 2000; Von Schacky, 2006).

In patients with psychiatric disorders, it has been demonstrated that a dose of up to 9.6 g is commonly safe and effective (Stoll et al., 1999), furthermore Hibbeln suggested that pregnant women may want to consume a minimum 650 mg/day of DHA and EPA (with a minimum 300 mg/day of DHA) to prevent postpartum depression (Hibbeln, 1998).

In mice, Tang et al. found that not only total dietary fat content but the forms of omega-3 fatty acids contributed to the effects of omega-3 fatty acids. DHA-PL (DHA and phospholipid) could increase DHA concentration in liver and brain during a short period and the increase of DHA level is much more significant in liver than in brain (Tang et al., 2012). The efficiency of PL (phospholipid) bound omega-3 is more significant than EE (ethyl ester) or FFA (free fatty acids) forms in increasing DHA concentration in tissues. This result was probably due to the difference in absorption and distribution of different omega-3 formulation (Tang et al., 2012). Other studies shown that long-term DHA intake could particularly increase cerebral DHA level (Suzuki et al., 1988; Hashimoto et al., 2005; Shirai et al., 2006; Gamoh et al., 1999).

1.1. Etiological hypotheses

PUFAs play central roles in different physiological functions (Lands, 2007; Lewis et al., 2011). Mechanisms that may underlie the association between omega 3 fatty acids insufficiency and the emergence of psychiatric disorders include several factors: a reduction of serotonin and dopamine levels (De la Presa and Innis, 1999; Levant et al., 2013; Schneider et al., 2016), an impaired neuronal migration and altered connectivity, timed apoptosis together with abnormalities in the dendritic arborization such that related to an irreversible disruption in those neuronal pathways involved in the regulation of behaviors (Sinclair et al., 2007; Hibbeln et al., 2004; Lakhani and Viera, 2008), neuroinflammatory processes (Faroqui et al., 2007; McGorry et al., 2014; Levant et al., 2013; Schneider et al., 2016), and hypothalamic pituitary adrenal axis dysregulation (Hibbeln et al., 2004; Levant et al., 2013; Schneider et al., 2016).

The relative abundance of specific fatty acids in membrane phospholipids affects cell physiology in a variety of ways (Levant et al., 2013). First, the fatty acid composition increases in the viscosity of the membrane. Thus changes in membrane composition influence the function of lipid rafts and proteins embedded in the membrane such as receptors, ion channels, and transporters (Salem et al., 2001; Stillwell et al., 2005). Second, free fatty acids modulate gene expression at the transcriptional level through the activation of transcription factors by activating nuclear receptors, such as the retinoid X receptor (RXR) and the peroxisome proliferator-activated receptors (PPAR) (Khan and Van den Heuvel, 2003; de Urquiza et al., 2000; Clarke et al., 1999). Moreover EPA and DHA may influence the signal transduction in the brain cells (Hibbeln et al., 1997) through the activation of peroxisome proliferator-activated receptors, inhibition of G-proteins and protein kinase C but also fundamental ion channels (Rudin, 1981). These fatty acids can also be metabolized into a variety of signaling mediators including as prostaglandins, thromboxanes, resolvins, maresins, and protectins (Salem et al., 2001; Horrocks and Faroqui, 2004; Bazan, 2005; Bannenberg et al., 2007; Bannenberg, 2010; Bazan, 2005; Horrocks and Faroqui, 2004; Salem et al., 2001; Serhan and Petasis, 2011). Accordingly, variation in membrane composition can alter the relative abundance of the various signaling molecules produced (Levant, 2013).

The accretion of DHA into brain phospholipids occurs primarily during late gestation and early neonatal life, though this varies somewhat between species (Clandinin et al., 1980; Green and Yavin,

1996). During this time, DHA is delivered to the developing offspring by the mother in utero prior to birth, and in breast milk, which is enriched in DHA, after birth (Innis, 1992, 2004).

Different studies show that brain n-3 PUFA status can be altered by either a failure of initial DHA accretion during development or the loss of DHA later in life (Levant et al., 2013). On an organism level, insufficient pre- and postnatal accretion of DHA during development does not produce any gross deficits in general health (Gordon, 1997). However, some decreases in visual, attentional, and intellectual development are reported (McNamara et al., 2006; Birch et al., 2000; Willatts et al., 1998; Makrides et al., 2010), as well as other neurobiological alterations, in particular the metabolism of the serotonin (which is involved in the regulation of mood, sleep, pleasure and related behaviors) (Araujo et al., 2010), that could predispose an individual toward depression or other psychiatric disorders (McNamara et al., 2006). Therefore lower dietary and tissue levels of n-3 PUFAs generally result in outcomes that are similar to those found in depression, while higher dietary or tissue levels of these fatty acids tend to have the opposite effect (Levant, 2013).

1.2. Suicidality and the potential role of PUFAs

Every year, almost one million people die by suicide around the world (World Health Organization, 2012). Suicide is the deliberate act of killing oneself whereas suicide attempt describes any nonfatal suicidal behavior, such as intentional self-inflicted poisoning, injury, or self-harm (Vijayakumar et al., 2016). Several researchers suggested that suicidal behavior may be associated with omega-3 fatty acid depletion (De Vriese et al., 2004; Hirayama, 1991; Huan et al., 2004; Sublette et al., 2006) and this depletion is reportedly associated with increased suicidal ideation in psychiatric patients (Tanskanen et al., 2001). Moreover, omega-3 insufficiency has been found in suicide attempters (Huan et al., 2004), as well as increased risk of prior (Huan et al., 2004) and future suicide attempts (Sublette et al., 2006). Furthermore an association between suicidal behavior and inflammation has been found (Brundin et al., 2016), and PUFAs have a marked effect on reducing inflammation.

Adequate consumption or prescription of PUFAs may have a role in attenuating suicidality, as clinical trials using omega-3 (in particular EPA) have been effective in treating MDD (Appleton et al., 2010), especially via adjunctive use with antidepressants (Sarris et al., 2016). It should be noted however that there is not always a direct link between suicidality and depression. Regardless, several studies have also shown, when compared to placebo, a reduction in depressive symptoms and significantly longer periods of remission appeared after adding to these patients 1–2 g of omega-3 fatty acids daily as EPA (Adams et al., 1996; Frangou et al., 2006; Leaf, 2001; Rudin, 1981; Hibbeln, 1998; Stoll et al., 1999; Parker et al., 2006). Balanzá-Martínez et al. (2011) summarized in a recent review that higher rates of bipolar spectrum disorders were associated with a diet with lower levels of omega 3. Furthermore, n-3 PUFAs have been demonstrated to exert an additional effect in patients with unipolar and bipolar depression when combined to other treatments (Sarris et al., 2016, 2012), as they seem to be effective on behavioral and neurochemical alterations associated with mood disorders including abnormal dopaminergic content and function, dysregulation in responses to stress, aggression, and depression (Balanzá-Martínez et al., 2011).

Reduction of omega-3 levels have been shown to be associated with increased rates of depression (Hibbeln and Salem, 1995; Tiemeier et al., 2003; Araujo et al., 2010) and the worsening of depressive symptoms (Brunner et al., 2002; Feart et al., 2008;

Mamalakis et al., 2002). In depressed patients, higher AA/EPA ratios have been found (Tiemeier et al., 2002; Maes et al., 1996; Maes et al., 1999) and the severity of depression has been reported to be associated with AA/EPA ratio in the phospholipids of the plasma and erythrocytes (Edwards et al., 1998; Adams et al., 1996). Peet et al. (1998) also reported a reduction of almost 50% in DHA in erythrocytes in individuals with MDD. Moreover, a higher concentration of AA plasma and lower concentrations of EPA were associated with greater depression and neurosis (Conklin et al., 2007). Furthermore, depressed individuals showed increased aggression and impulsivity scores and reduced lnEPA (Ln-transformed EPA) relative to healthy controls, but no differences regarding aggression, impulsivity and lnEPA have been detected between depressed subjects who did attempt suicide and those who did not (Beier et al., 2014). While previous papers have reviewed the relationship between depression, suicide, and PUFAs, to our knowledge, no specific systematic review to date has been conducted on PUFAs as a modifying factor of suicidality (ideation, attempted or completed suicide). Considering this, we conducted a specialized systematic review aimed to investigate the relation between PUFAs and suicidal behavior.

2. Methods

2.1. Selection criteria and quality assessment

We aimed to provide a novel and timely systematic review concerning the association between PUFAs and suicidal behavior in mood disorders, using the PRISMA statement for reporting systematic reviews (Liberati et al., 2009). We conducted a MedLine, Excerpta Medica, PsycLit, PsycInfo, and Index Medicus search to identify all papers and book chapters in English on this area for the period of January 1997 to June 2015 was carried out.

The following search terms were used: “PUFAs”* (which comprises: omega-3, omega-6, polyunsaturated fatty acids and other fatty acid-related terms) “suicide”* (which comprises: suicide behavior, suicide attempts, suicide risk) and “mood disorders”* (which comprises: major depressive disorder, depression, bipolar disorder and other mood disorders-related terms). Moreover, we consulted textbooks on psychiatry. Only articles published in English peer-reviewed journals were selected, consisting of epidemiological studies, post-mortem studies, or prospective clinical trials (i.e. for suicide prevention or reduction of suicidal ideation) were included. No criteria were set for sample size, gender, age, or ethnicity of participants. PUFA status for epidemiological or post-mortem status needed to be assessed via acceptable methodology (e.g. cell or serum levels or history intake of fish), while clinical studies needed to have an adequate control group (e.g. placebo).

Full-text articles were evaluated for inclusion if considered to be potentially relevant via a review of the abstract. Consultations with the senior authors were used when any discrepancies occurred between the two reviewers who, blind to each other, evaluated the studies for the possible inclusion. Two reviewers (GD, LL) independently examined all citations of studies obtained using the search and grouped them based on the main topic of each paper. A detailed discussion with the senior author (MP) who also independently assessed all the articles and categorized them according to the major areas of interest identified by the reviewers occurred in the case of any disagreement. In the case of any doubts, the article was put on the list of studies awaiting assessment pending the acquisition of detailed information.

3. Results

3.1. Search results

After removing duplicates, the combined search strategy yielded a total of 436 articles, of which the most relevant were selected for the present review (see Fig. 2). After an initial review process, 226 studies were excluded from the 436 (only 7 studies were written in languages other than English). During the second stage of the screening process, two additional reviewers read the full-text articles coding them according to methodology. This left 42 relevant remaining clinical studies. After a final review, 18 full-text articles were found to meet our inclusion criteria to be included in the final review (24 additional articles were excluded due to the low-relevance to the main theme).

3.2. Study design and quality assessment

A quality assessment was carried out as reported in Table 1. The following criteria were used to assess the quality of epidemiological studies: I) representativeness of the sample in the general population (> 1000 subjects = 1 point); II) presence of a control group in clinical trials (0 point: no control group, 1 point: control group < 30 subjects, 2 points: control group > 30 subjects); III) $n > 1000$ subjects/treatment group (0 point: subjects < 1000, 1 point: subjects 1000 > $x < 2000$, 2 points: subjects > 2000); IV) duration of follow up (0: no follow-up, 1: follow-up < 1 year, 2 points: follow-up > 1 year); V) evidence based measures of diagnostic assessment (1: self-reported questionnaire, telephonic interview or 2 points: assessment by psychiatric); VI) Data Presentation (1: the article is not clear, 2 points: the article is clear); VII) evidence-based measures assessing PUFAs depletion in suicidal behavior (1: post-mortem study, correlation without biochemical analysis or 2 points). Possible quality ratings could range from 0 to 13; however, the ratings of this systematic review ranged from 3 to 11, with the mean average quality rating being 6.9.

3.3. Clinical association with suicidal behaviors

3.3.1. The association between PUFA dietary intake and suicide risk: epidemiological findings of fish consumption

Data from epidemiological studies exploring the association between PUFA dietary intake and suicide risk reported mixed but largely unresponsive results.

A major Japanese prospective cohort study conducted on 101,507 subjects (Poudel-Tandukar et al., 2011), found there was no supportive evidence for the association between the lower suicide risk and a high intake of fish, EPA, and DHA in Japanese men and women. Their study found that overall, 213 men and 85 women completed suicide during 403,019 and 473,351 person-years of follow-up. Multivariate Hazard Ratios (HRs; 95% CI) of completed suicides for the highest versus lowest quintile of fish intake resulted 0.95 (0.60–1.49) and 1.20 (0.58–2.47) for men and women, respectively. However, it was notably revealed that women with very low consumption of fish showed a higher risk of suicide death and HRs (95% CI) were 3.41 (1.36–8.51) in the case of individuals in 0–5th percentile versus middle quintile of 3.41 (1.36–8.51) (Poudel-Tandukar et al., 2011).

Also, in another large cohort study with a long follow up period, n-3 PUFAs or fish consumption were not found to reduce the risk of completed suicide (Tsai et al., 2014). Overall, 287 suicide events were reported during the course of 3,511,768 person-years of follow-

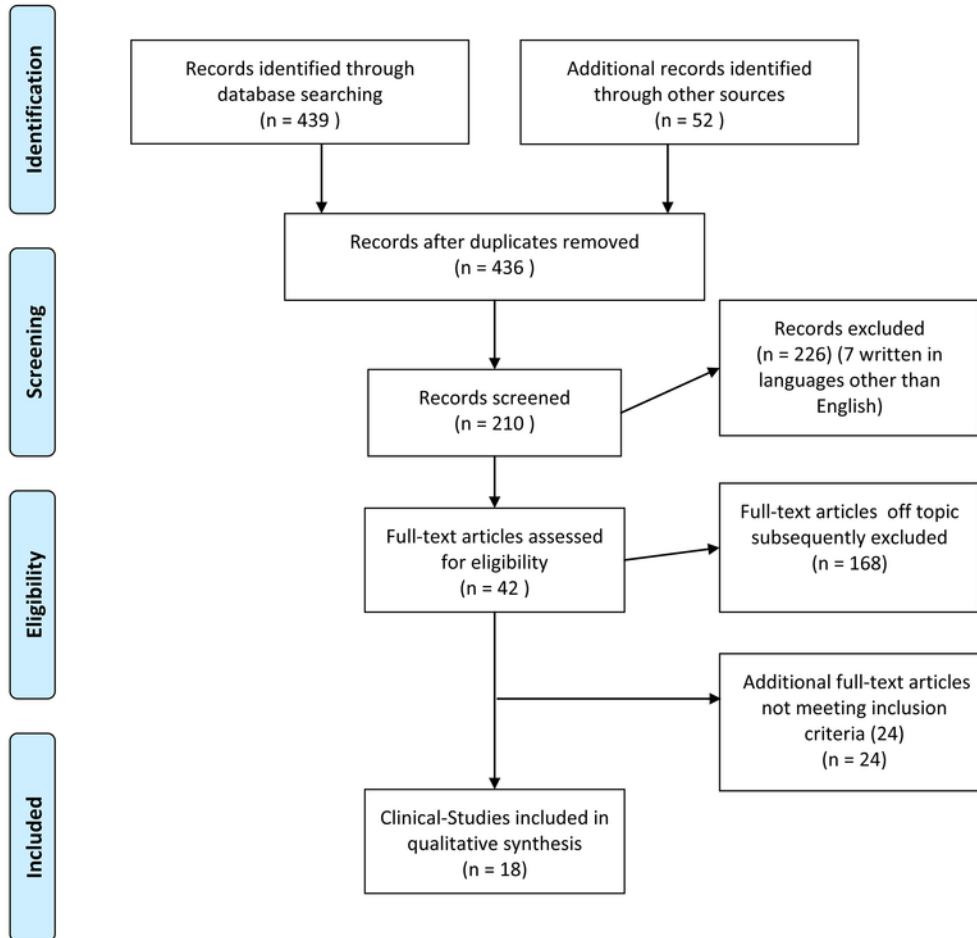


Fig. 2. Stages of the screening process.

up across the 3 cohorts. It was also revealed that each 1 g/day of α -linolenic acid intake was associated with a non-significant relative risk for suicide mortality of 0.88 (95% confidence interval (CI): 0.69, 1.13). However each 0.3 g/day of EPA + DHA intake with conferred a significantly greater protective relative risk of 1.21 (95% CI: 1.05, 1.39), respectively. The relative risk for each 1 g/day of total n-3 intake was 1.43 (95% CI: 1.01, 2.02) as well. While the study demonstrated a reduced risk of suicide mortality in subjects with greater linoleic acid consumption, the multivariable regression models however revealed that, this relationship had a non-statistically significant trend for reduced risk of suicide mortality across linoleic acid intake quartiles (Ptrend = 0.09). In particular the authors reported that every 5 g/day of linoleic acid consumption was associated with a relative risk of 0.67 (95% CI: 0.48, 0.95) but also this findings are non-statistically significant. Conversely, a non-significant increased mortality for suicide was associated with greater arachidonic acid consumption (RR: 1.15; 95% CI: 0.92, 1.44), and a null association for n-6 PUFA consumption (RR: 0.76, 95% CI: 0.56, 1.03). When disaggregated by cohort, men most strongly exhibited the reduced risks from linoleic acid consumption. Across categories of consumption frequency, a non-significant trend for the decrease of suicide mortality (Ptrend = 0.80) was found (Tsai et al., 2014). Hakkarainen et al. (2004) conducted a population-based trial in a sample of 29,133 men ages 50 to 69 years in Finland and found that there were no associations between the dietary intake of omega-3 fatty acids or fish con-

sumption and depressed mood, major depressive episodes, or suicidal behavior.

3.3.2. The association between PUFA dietary intake and suicide risk: data from experimental studies

In a study consisting of 23 volunteers, De Vriese et al. (2004) demonstrated that there was a significant variation in the seasonal rhythm of arachidonic acid (AA; mean SD 5.05 in fall, 4.55 in winter, 4.81 in spring and 4.81 in summer), EPA (mean SD 0.46 in fall, 0.39 in winter, 0.44 in spring, 0.55 in summer), DHA (mean SD 1.78 in fall, 1.52 in winter, 1.81 in spring, 1.87 in summer), and total omega-3 blood serum levels (mean SD 3.75 in fall, 3.30 in winter, 3.65 in spring, 3.81 in summer), which were all elevated around August–September and lower in winter. Furthermore, there is a significant negative correlation between delta AA (delta AA = AA, 2 weeks earlier minus the actual AA) ($r = -0.63, p = 0.00001$), delta EPA ($r = -0.64, p = 0.00001$) and delta DHA ($r = -0.58, p = 0.00005$), and the occurrence of violent, but not nonviolent, suicide. The lower the PUFA levels some weeks earlier and the higher the increase over the previous weeks before suicide, the higher the number of suicide deaths. Thus, the seasonal variation in EPA or DHA may partially be implicated in the seasonality in the occurrence of violent suicide deaths (De Vriese et al., 2004). This may potentially be related to dietary changes affecting PUFA consumption across the seasons.

Table 1
Summary of studies included in the review.

Post-mortem studies							
Study	Quality score	Study design	Eventual follow-up	Participants	Main findings	Limitations	Ref.
McNamara and Yanhong (2011)	I = 0 II = 1 III = 0 IV = 0 V = 2 VI = 2 VII = 1 Total score = 6	Observational study	No	N = 20 subjects 10 MDD patients 10 non-psychiatric controls	Patients with MDD exhibited reduced expression of key genes involved in LC-PUFA biosynthesis, FADS1, FADS2, and HELO1, and monounsaturated fatty acid biosynthesis, and SCD, in the postmortem frontal cortex compared with controls. There were no significant gender effects, and relative reductions in FADS1, HELO1. Also, SCD expression was greater in patients that did not commit suicide compared to patients who did commit suicide.	Small size of sample. The result is not generalizable for all MDD patients. The MDD patients were receiving antidepressant medications. The study examined one brain region which may not be representative of other brain regions in terms of fatty acid composition.	[35]
McNamara et al. (2013)	I = 0 II = 1 III = 0 IV = 0 V = 2 VI = 2 VII = 1 Total score = 5	Observational study	No	N = 40 subjects 20 suicide victims 20 adults controls	The DHA concentration and composition data were positively correlated, the deficit in DHA composition observed in depressed suicide victims compared with controls without cardiovascular disease (14%) did not reach statistical significance ($p \leq 0.1$).	It is not possible to trace the fish intake. The study analyzed postmortem subjects, therefore the results are not generalizable to the general population. The study examined one brain region which may not be representative of other brain regions in terms of fatty acid composition. Small size of sample.	[36]
Hamazaki et al. (2015)	I = 0 II = 1 III = 0 IV = 0 V = 1 VI = 2 VII = 1 Total score = 5	Observational study	No	N = 60 post-mortem subjects N:15 patients with schizophrenia N:15 patients with bipolar disorder N:15 patients with MDD N:15 unaffected controls	The study found no significant differences in the levels of PUFAs or other fatty acids in the prefrontal cortex (BA8) between patients and controls. Comparison between suicide and non-suicide cases showed no significant differences in any individual fatty acids; however, significant decreases were seen in total saturated fatty acid sin suicide cases (1.4%, $p \leq 0.05$).	Small sample size. The severity of psychiatric symptoms at the time of death is not known.	[38]
McNamara et al. (2007a,b)	I = 0 II = 1 III = 0 IV = 0 V = 2 VI = 2 VII = 1 Total score = 6	Observational study	No	N = 42 subjects 15 MDD 27 age-matched normal controls	Significantly lower omega-3 fatty acid concentrations in MDD patients. There were no differences in OFC DHA concentrations in MDD patients that committed suicide ($n = 7$) versus MDD Patients that died from cardiopulmonary-related diseases ($n = 7$)	Small number of subjects. There is no information available regarding the diets of MDD patients or normal controls. The severity of depressive symptoms at the time of death is not known.	[37]
McNamara et al. (2009)	I = 0 II = 1 III = 0 IV = 0 V = 2 VI = 2 VII = 1 Total score = 6	Observational study	No	N = 40 subjects 20 adolescents suicide victims; 20 age-matched controls	PFC DHA (prefrontal cortex docosahexaenoic acid) composition did not differ between suicide victims and normal controls regardless of gender. Adolescent male and female suicide victims do not exhibit DHA deficits in the postmortem PFC (BA10) relative to age-matched controls.	The study did not analyze subject erythrocytes or plasma to evaluate the relationship with PFC fatty acid composition. The study examined one brain region which may not be representative of other brain regions in terms of fatty acid composition. Small number of subjects.	[39]

Table 1 (Continued)

Post-mortem studies							
Study	Quality score	Study design	Eventual follow-up	Participants	Main findings	Limitations	Ref.
McNamara et al. (2008)	I = 0 II = 1 III = 0 IV = 0 V = 2 VI = 2 VII = 1 Total score = 6	Observational study	No	N = 37 subjects. 18 patients with BD 19 normal controls	In bipolar patients that committed suicide ($n = 11$), the only fatty acid that exhibited a significant alteration relative to normal controls was DHA, which exhibited a modest reduction (-16% , $p = 0.03$). In bipolar patients who died for other causes ($n = 7$), larger OFC DHA deficits were observed (-35% , $p = 0.0006$) and alterations in several additional fatty acids were observed.	No information was available regarding the diets of bipolar patients or normal controls. The study examined one brain region which may be not representative of other brain regions in terms of fatty acid composition. Manic or depressive symptom severity at the time of death could be not ascertained. The small number of patients in the drug-free group ($n = 3$) may not be representative of all drug-free bipolar patients.	[40]
Observational studies							
Study	Quality score	Study design	Eventual follow-up	Participants	Main findings	Limitations	Ref.
De Vriese et al. (2003)	I = 0 II = 1 III = 0 IV = 0 V = 2 VI = 2 VII = 1 Total score = 6	Observational study	No	N = 23 subjects 12 men 11 women	The study shows the significant correlation between the seasonality in PUFAs, such as EPA and DHA, and the occurrence of violent suicide. Decreased EPA and DHA may be related to the pathophysiology of suicide and depression.	The study was conducted in a single geographic area. Small size of sample.	[22]
Huan et al. (2004)	I = 0 II = 2 III = 0 IV = 0 V = 2 VI = 2 VII = 1 Total score = 7	Observational study (case control study)	No	N = 200 subjects 100 suicide attempt patients 100 control subjects	The mean levels of EPA, DHA, and total n-3 fatty acids were significantly lower in the suicide attempt group than in the control group. In contrast, the levels of saturated fatty acids, monounsaturated fatty acids, and n-6 polyunsaturated fatty acids did not differ significantly between the two groups except for stearic acid, which was slightly but significantly higher in the suicide attempt group. There were no associations between the frequency of fish intake and the risk of suicide attempt.	All 100 patients had attempted suicide. The study was conducted in a single geographic area.	[24]
Sublette et al. (2006)	I = 0 II = 1 III = 0 IV = 2 V = 2 VI = 2 VII = 2 Total score = 9	Observational study (longitudinal)	2 years	N = 33 subjects Medication-free depressed patients	The study shows that low docosahexaenoic acid percentages of total phospholipid fatty acids and elevated omega-6/omega-3 ratio predict suicidal behavior in major depression. Moreover, plasma polyunsaturated fatty acid status may mediate the effects of age and suicidal ideation on the outcome of suicide attempt.	The study cannot be determined whether psychopathology affected dietary habits or vice versa. Small size of sample.	[25]
Lewis et al. (2011)	I = 1 II = 2 III = 1 IV = 0 V = 1 VI = 2 VII = 1 Total score = 8	Case-control study	No	N = 1600 subjects 800 suicide deaths 800 controls Active duty US military (between 2002 and 2008)	Low docosahexaenoic acid (DHA) status is a significant risk factor for suicide death among active duty US military.	Inability to characterize neuropsychiatric symptoms, stress exposure, traumatic brain injury, alcohol use, or other potential risk factors, and assessment of reverse causality.	[33]

Table 1 (Continued)

Observational studies							
Study	Quality score	Study design	Eventual follow-up	Participants	Main findings	Limitations	Ref.
Beier et al. (2014)	I = 0 II = 2 III = 0 IV = 0 V = 2 VI = 2 VII = 1 Total score = 7	Observational study	No	N = 83 subjects N:48 MDD patients N:35 healthy volunteers	The study demonstrates that substance use disorder comorbidity robustly drove associations between low plasma EPA and high trait aggression and impulsivity in MDD patients. Aggression and impulsivity scores were higher, and in EPA was lower, in MDD patients compared with HV, but did not differ between MDD suicide attempters and non-attempters.	Small sample size. Clinically diverse group (regarding current psychiatric status and medication history). No information about the participants' total dietary intake and level of activity.	[34]
Haghighi et al. (2015)	I = 0 II = 2 III = 0 IV = 0 V = 2 VI = 2 VII = 2 Total score = 8	Observational study	No	N = 120 subjects 61 MDD subjects (22 suicide attempters and 39 non-attempters) 59 controls	There are significant differences between MDD and healthy volunteer subjects, with respect to PUFAs. DNA methylation of genes involved in n-3 PUFA biosynthesis was associated with MDD and suicide risk.	Clinically diverse group (proportion of Caucasian subjects was higher in the MDD group than among volunteers). No follow up (suicide risk long-term).	[41]
Cross-sectional studies							
Study	Quality score	Study design	Eventual follow-up	Participants	Main findings	Limitations	Ref.
Evans et al. (2012)	I = 0 II = 0 III = 0 IV = 0 V = 1 VI = 2 VII = 1 Total score = 4	Cross-sectional study	No	N = 27 subjects Bipolar patients	n-3 and n-6 lipid profiles correlate with Aspects of the five factor personality model that have themselves been associated with suicidal behavior.	Small sample size. Clinically diverse group (regarding current status and medication history).	[5]
Vaz et al. (2014)	I = 0 II = 2 III = 0 IV = 1 V = 2 VI = 2 VII = 2 Total score = 9	Cross-sectional study (for cohort study)	Yes	N = 234 (pregnant women)	Higher serum status of arachidonic acid [AA] and adrenic acid [AdA], two omega-6 fatty acids, were associated with greater likelihood of suicide risk and major depressive episode among pregnant Brazilian women independently of confounding variables.	The study was conducted in a single geographic area. Only women between 20 and 40 years of age. These results derive from women of low socioeconomic background. No assessment before and after pregnancy.	[34]
Hibbeln et al. (1997)	I = 0 II = 1 III = 0 IV = 0 V = 1 VI = 2 VII = 0 Total score = 4	Cross-sectional study	No	N = 45 subjects	The study suggest that long-chain polyunsaturates predict measures of serotonergic neurotransmission, specifically CSF 5-HIAA (Low concentrations of cerebrospinal fluid %-HIAA seem to be related to suicide and violence).	The study analyzed only healthy controls. There was not the assessment of the risk of suicide. There was not a psychiatric assessment. Small size of sample.	[30]

Prospective/clinical trials

Study	Quality score	Study design	Eventual follow-up	Participants	Main findings	Limitations	Ref.
Poudel-Tandukar et al. (2011)	I = 1 II = 2 III = 2 IV = 2 V = 1 VI = 2 VII = 1 Total score = 11	Prospective study	Yes	N = 101,507 subjects 47,351 men 54,156 women (aged 40–69 years)	The study provides no evidence to support the hypothesis that a high intake of fish, EPA, and DHA reduces the risk of suicide in Japanese men and women.	The results are dependent to self-reported questionnaire. The measurement of fish intake may not be sufficiently accurate and consistent to detect an association with suicide. The study cohort included subjects with a history of chronic disease or medication and stress, who may have altered dietary intake of fish, EPA or DHA. Depression at the time of baseline dietary assessment was not assessed in the study. Subjects were middle aged population and they do not represent a random sample of the Japanese population.	[28]
Hallahan et al. (2007)	I = 0 II = 1 III = 0 IV = 1 V = 2 VI = 2 VII = 2 Total score = 8	Randomized controlled trial	Yes	N = 49 subjects. Patients after an act of repeated self-harm	Reversal of an n-3 EPA deficit improved psychological status in such patients with self-harm. The proportion of self-harm episodes was actually higher during the study period in the patients on active drug (7/22, 38.2%) compared with those in the placebo group (7/27, 25.9%), although the difference was not statistically significant.	Small sample size.	[31]
Tsai et al. (2014)	I = 1 II = 2 III = 2 IV = 2 V = 1 VI = 2 VII = 1 Total score = 11	Cohort study	Yes	N = 114,521 subjects 42,290 men 72,231 women	Greater fish intake did not have a statistically significant association with suicide mortality. Across categories of intake frequency, there was a non-statistically significant reduction in risk of suicide mortality.	Clinically diverse group (regarding current status and medication history). The study excluded persons younger than 29 years of age.	[29]

Legend:

BA8: prefrontal cortex.
DHA: docosahexaenoic acid.
FADS1: delta5 desaturase.
FADS2: delta6 desaturase.
HELO1: elongase.
LC-PUFA: long-chain polyunsaturated fatty acids.
MDD: Major Depressive Disorder.
OFC DHA: orbitofrontal cortex docosahexaenoic acid.
SCD: stearyl-CoA desaturase.
EPA: eicosapentaenoic acid.
HV: healthy volunteer.
PUFA: polyunsaturated fatty acids.
AA: arachidonic acid.
AdA: adrenic acid.
CSF: cerebrospinal fluid.
5-HIAA: 5-Hydroxyindoleacetic acid.

Hibbeln et al. (1997) investigated the association between suicidal behavior, cholesterol and fatty acids in 45 healthy controls. The researchers found that plasma total cholesterol did not predict CSF 5-HIAA (cerebrospinal fluid 5-hydroxy-indole-acetic acid) or CSF HVA (cerebrospinal fluid homovanillic acid) concentration. One of the strongest predictors of CSF 5-HIAA ($r = 0.41$, $p < 0.005$) and of CSF HVA ($r = 0.47$, $p < 0.001$) was the total long-chain polyunsaturated fatty acid serum level. Furthermore, low concentrations of HIAA in cerebrospinal fluid seem to be associated with suicide and violence.

Huan et al. (2004) examined the levels of PUFAs in the Red Blood Cells of healthy subjects and suicide attempters (the assessment was done within 1 week from the date of the suicide attempt). Relative to the control group ($n = 100$), suicide attempters ($n = 100$) demonstrated significantly lower levels of EPA (0.74–0.52% vs.

1.06–0.62%, $p = 0.0001$), DHA (4.4–1.6 vs. 5.3–1.7, $p = 0.003$) and total omega-3 fatty acids (8.5–2.4 vs. 9.9–2.9, $p = 0.0002$), and higher levels of stearic acid in RBC. The suicide attempters group and control group did not significantly differ regarding the mean levels of saturated fatty acids, monounsaturated fatty acids or omega-6 polyunsaturated fatty acids. Given that there were no associations found between RBC omega-3 fatty acids and the Suicide Intent Scale, Hamilton Rating Scale for Depression, or impulsivity, the authors concluded that suicide risk was not associated with the frequency of fish consumption (Huan et al., 2004).

The intake of fatty acid in the prevention of risk of suicide was also examined by Hallahan et al. (2007). Specifically, he found that patients who received eicosapentaenoic acid in addition to standard psychiatric care showed a reduction in suicide risk (Hallahan et al., 2007). In contrast, three other studies showed that there was no asso-

ciation between fatty acids consumption and suicide risk, and the use of fatty acid did not reduce suicide risk in the general population (Huan et al., 2004; Poudel-Tandukar et al., 2011; Tsai et al., 2014).

3.3.3. Correlation between PUFAs levels and suicidal behavior in depressed patients

Other studies have also been conducted on this topic in depressed patients. For example, in a 2-year follow-up study of 33 medication-free depression patients, Sublette et al. (2006) found that a higher omega-6/omega-3 ratio ($p = 0.002$, HR = 1.36) and a low percentage of DHA ($p = 0.002$, HR = 0.29) predicted suicidal behavior (Sublette et al., 2006). Moreover, in a case-control study, Hallahan et al. (2007) assessed the efficacy of n-3 PUFAs intake in 49 subjects with a history of recurrent self-harm. Specifically, together with the standard psychiatric care, 22 patients received EPA for 12 weeks. At the end of treatment, individuals with n-3 PUFA reported significant improvements in BDI scores ($p = 0.04$, 95% CI = 12.1–22–9). More patients in the n-3 PUFA group showed a > 50% ($p = 0.001$) and 70% ($p = 0.01$) reduction (response and remission respectively) in symptoms. Furthermore, more participants reported no suicidal ideation in the n-3 PUFA group ($n = 14$) than the placebo group ($n = 8$, $p = 0.018$). Logistic regression indicated that neither the irritability and aggression sub-scale (both of which demonstrated no difference between the two groups) nor the depression scores, had any effect on the suicidality subscale (Hallahan et al., 2007).

A recent study (Beier et al., 2014) compared 35 healthy volunteers and 48 patients with MDD, with and without concomitant substance abuse disorder (SUD). Aggression and impulsivity scores were found associated with plasma lnEPA (ln-transformed EPA) after controlling for diagnostic status (in particular MDD with and without history of SUD), and gender. Furthermore, an interesting correlation was found between lnEPA and aggression or impulsivity in subjects with MDD and comorbid SUD. In particular, lnAA: EPA ratio and aggression were found to be associated ($p = 0.001$); also, the diagnostic status and lnAA:EPA ratio were reported to be correlated ($p = 0.002$). In addition a trend ($p = 0.094$) toward a positive correlation emerged in the lnAA:EPA-ratio concerning impulsivity. Plasma lnDHA and aggression or impulsivity scores were reported to be not correlated as well. In conclusion, increased aggression and impulsivity scores and decreased lnEPA (Ln-transformed EPA) were found in MDD subjects relative to healthy volunteers, but no difference emerged between depressed individuals who attempted suicide compared to those who did not.

3.3.4. Correlation between PUFAs levels and suicidal behavior in patients with bipolar disorder

While several studies explored the correlation between PUFAs level and suicide in unipolar depressed subjects, the only study to our knowledge investigating this correlation in participants with bipolar depression was that of Evans et al. (2012) who examined plasma levels of both n-3 and n-6 fatty acids in a sample of 27 patients with bipolar disorder (BD) and found associations between suicidal history and lipid profiles. They noted that subjects who attempted suicide showed reduced levels of the long chain n6, AA when compared to those who did not attempt suicide; interestingly, they hypothesized a protective effect of higher serum PUFA levels ($p = 0.026$).

3.3.5. The association between PUFAs dietary intake and suicide risk in specific populations

Lewis et al. (2011) investigated total serum fatty acid compositions in a sample of 800 active duty United States (US) military suicide deaths compared with 800 matched controls (2002–2008). They

reported that each standard deviation (SD) lower DHA was associated with a 14% greater risk of suicide (OR = 1.14, 95% CI; 1.02–1.27, $p < 0.03$), in adjusted logistic regressions. Among men, risk of suicide death was 62% greater with low serum DHA status (OR = 1.62, 95% CI, 1.12–2.34, $p < 0.01$) comparing DHA below 1.75% ($n = 1.389$) to above this serum level ($n = 141$). In addition, military who reported having seen wounded, dead or killed coalition show a risk of suicide of 54% greater (OR = 1.54, 95% CI; 1.12–2.12, $p < 0.007$).

In a recent study on Brazilian pregnant women, Vaz et al. (2014) found that the higher suicide risk has been reported among women having increased serum status of arachidonic acid [AA (20:4n-6): OR = 1.45, 95% CI 1.02–2.07] and adrenic acid [AdA (22:4 n-6): OR = 1.43, 95% CI 1.01–2.04], and for major depressive episode: AA [OR = 1.47, 95% CI 1.03–2.10], and AdA [OR = 1.59, 95% CI 1.09–2.32]. In multivariate models of suicide risk, each standard deviation of higher arachidonic acid (AA; 20:4 n-6) and adrenic acid (AdA; 22:4 n-6) were associated, respectively, with 45% (OR = 1.45; 95% CI: 1.02–2.07) and 43% (OR = 1.43; 95% CI: 1.01–2.04) increased chances of suicide risk after controlling for parity, marital status, and gestational week.

3.4. Post-mortem studies

3.4.1. Correlation between PUFAs levels and suicidal behavior in depressed patients

McNamara investigated the gene expression linked to LC-PUFA biosynthesis (FADS1, FADS2, and HMOX1, SCD) determining the gene expression in frozen (unfixed) postmortem prefrontal cortex gray matter in a sample of 10 healthy controls compared with 10 patients with previous MDD. The main findings revealed that both central and peripheral depletion in long-chain PUFAs, (in particular omega-3 fatty acid insufficiency) was associated with MDD. MDD subjects also exhibited a decreased expression of FADS1, FADS2, and HMOX1, and SCD in the postmortem frontal cortex as compared to controls ($- 27%$, $p = 0.009$, Cohen's $d = 1.3$) (McNamara and Yanhong, 2011).

In a subsequent postmortem observational study, McNamara and Yanhong (2011) found that there was a non-significant trend for lower DHA concentrations in depressed suicide victims compared with all controls ($- 10%$, $p = 0.06$, $d = 0.5$). Furthermore, depressed suicide victims ($n = 20$) reported reduced concentrations of DHA in the prefrontal cortex compared to the control groups without cardiovascular disease ($n = 20$) ($- 14%$, $p = 0.03$, $d = 0.7$) (McNamara et al., 2013). Conversely, a previous smaller postmortem study (McNamara et al., 2007b) showed that there were not differences in DHA concentration concerning orbitofrontal cortex of seven MDD subjects who completed suicide relative to seven individuals who died from cardiopulmonary-related diseases ($p = 0.147$).

In a subsequent post-mortem study, Hamazaki et al. (2015) did not find significant difference of the levels of PUFAs (n-3, n-6 and n-6/n-3), saturated fatty acids, or monounsaturated fatty acid, in the BA8 region of the prefrontal cortex between individuals with MDD and healthy controls. In MDD, a negative association was found between age and arachidonic acid (20:4n-6) and positive associations were observed between age and both nervonic acid (24:1n-9) (saturated fatty acid) and monounsaturated fatty acids. Although no significant differences were reported regarding any specific fatty acids between subjects who died by suicide and those who did not, significant decreases were seen in total saturated fatty acids in suicide cases ($- 1.4%$, $p = 0.05$).

McNamara et al. (2009) also evaluated the impact of PUFA levels on suicidal behavior in a group of adolescents. The researchers compared 20 adolescents without a history of depression with 20 depressed adolescents who died by suicide. The depressed/suicide group did not show a significant DHA deficit or differences in this fatty acid composition in the prefrontal cortex compared to the non-depressed control. They also reported no significant correlations in the total sample between DHA composition and brain pH ($r = 0.24$, $p = 0.15$), or post-mortem interval ($r = 0.02$, $p = 0.92$), or other fatty acid compositions and these variables (all $p > 0.05$), except for docosapentaenoic acid (DPA; 22:5 n-6) for which a positive correlation with postmortem interval emerged ($r = 0.35$, $p = 0.03$).

3.4.2. Correlation between PUFAs levels and suicidal behavior in patients with bipolar disorder

In a post-mortem study (McNamara et al., 2008), only a deficit of DHA (16%, $p = 0.03$) in the orbitofrontal cortex was found in suicidal bipolar patients ($n = 11$) relative to normal control; whereas in bipolar patients that died of other causes ($n = 7$) was observed a larger deficit of DHA (-35% , $p = 0.0006$), palmitic acid (-16% , $p = 0.0026$), stearic acid (-8% , $p = 0.0001$), cis-vaccenic acid ($+21\%$, $p \leq 0.0001$), oleic acid ($+22\%$, $p = 0.001$) and arachidonic acid (-22% , $p = 0.0001$).

In a subsequent study, no differences concerning levels of PUFAs or other fatty acids have been identified in the BA8 region of the prefrontal cortex between patients with BD ($n = 15$) (area % total saturated fatty acid median: 47.46; area% total monounsaturated fatty acids median: 21.83; area% total n-3 polyunsaturated fatty acids median: 15.34, area% total n-6 polyunsaturated fatty acids median 15.69) and healthy controls ($n = 15$) (area% total saturated fatty acid median: 47.66; area% total monounsaturated fatty acids median: 20.88; area% total n-3 polyunsaturated fatty acids median: 16.17, area% total n-6 polyunsaturated fatty acids median 15.47) as well as between suicide and non-suicide cases according to a recent post-mortem study (Hamazaki et al., 2015). The comparison between suicide and non-suicide cases showed no significant difference in any individual fatty acids; however, significant decreases were seen in total saturated fatty acid levels in suicide cases (-1.4% of total fatty acids, $p = 0.05$).

A recent observational study (Saunders et al., 2015) compared biomarkers between healthy controls ($n = 31$) and symptomatic subjects with bipolar disorder ($n = 27$) when ill and after symptomatic recovery (follow-up). Exploratory comparison showed lower un-esterified (UE)/esterified (E) EPA in the bipolar disorder than the healthy controls group ($p < 0.0001$). At follow-up in the bipolar disorder group, UE, E, docosahexaenoic acid (DHA)/alpha-linolenic acid (ALA), and UE eicosapentaenoic acid (EPA)/alpha-linolenic acid (ALA) were decreased ($p < 0.002$). Exploratory correlations of clinical variables revealed that mania severity and suicidality were positively correlated with UE/E EPA ratio.

3.4.3. Correlation between PUFAs levels and suicidal behavior according to genetic studies

In an important genetic study, Haghghi et al. (2015) reported an association regarding both MDD and suicide risk and DNA methylation of genes involved in n-3 PUFA biosynthesis: long-term changes in the epigenome may be associated with PUFA imbalances that were associated with suicidal behavior. In particular, compared to depressed individuals who did not attempt suicide, the authors reported differences regarding 22:4n-6 and its ratio with 20:4n-6 associated with elongase (Elovl5) activity in subjects who had an history of suicide attempts, although these differences did not result significant af-

ter adjustment for multiple testing. Those who did attempt suicide, both increased levels in the 22:4n-6 and its ratio with 20:4n-6, and trend associations with increased 22:5n-3 (DPA) levels and reduced ratios of 20:3n-6/18:3n-6 were associated with Elovl5 activity. Reduced CpG methylation levels within the downstream Elovl5 TSS region ($p = 0.0028$ adjusted) were also found in depressed individuals who attempted suicide, whereas increased methylation in the upstream Elovl5 region emerged relative to depressed subjects who did not attempt suicide ($p = 0.0036$). Finally, depressed patients who attempted suicide showed a higher Elovl5 methylation in the upstream region and a decreased methylation in the downstream region. This suggested that opposite functional effects may be exerted by methylation in these two shore regions, highlighting the existence of potential epigenetic markers of suicide risk.

Levey et al., 2016 identified genes that change in expression between no suicidal ideation and high suicidal ideation states ($n = 12$ participants out of a cohort of 51 women psychiatric participants followed longitudinally, with diagnoses of bipolar disorder, depression, schizoaffective disorder and schizophrenia). Although preliminary, such study investigated suicidality in women and found that docosahexaenoic acid signaling was one of the top biological pathways overrepresented in validated biomarkers. These findings are important in perspective of potential therapeutic and prophylactic benefits of omega-3 fatty acids.

4. Discussion

4.1. Summary of findings

Various studies reviewed have found a correlation between suicidal behavior and the serum or RBC level of fatty acids, however overall this association is not confirmed due to several null study results. In respect to supportive findings, both a higher omega-6/omega-3 ratio and lower percentage of DHA of the total phospholipids fatty acids has been shown to predict suicidal behavior in depressed patients without medication. Moreover, a higher serum status of arachidonic acid and adrenic acid (both are omega-6 PUFAs) has been shown to be correlated with prevalence of suicide risk in pregnant women. In addition, significantly reduced levels of EPA, DHA, and total omega 3 fatty acids together with higher levels of stearic acid have been reported in suicide attempters relative to controls. However there were studies that provided contradictory findings, with some revealing no association between fatty acid levels in large epidemiological analyses. Of note, three large studies showed that there was no association between fatty acids consumption and suicide risk, and the use of fatty acid did not reduce suicide risk in the general population (Huan et al., 2004; Poudel-Tandukar et al., 2011; Tsai et al., 2014).

Post-mortem studies revealed mixed evidence for the association between fatty acids, suicide risk and psychiatric illness; with some data showing the concentration of DHA being reduced in the orbitofrontal cortex of post-mortem subjects with MDD and BD. As detailed above, a recent genetic study showed that both MDD and suicide risk were related to DNA methylation of genes involved in n-3 PUFA biosynthesis. In particular, an increased Elovl5 methylation of the upstream region and a reduced Elovl5 methylation of the downstream region may be reported in depressed suicide attempters. Importantly, the methylation of these two shore regions may play a different (opposite) functional effect, and PUFA long-term imbalances could directly induce key changes which may be associated with the emergence of suicidal behavior. Furthermore, a correlation between both central and peripheral reductions of long-chain polyunsaturated

fatty acids (LC-PUFA) and MDD has been found as well as a reduced expression of FADS1, FADS2, and SCD HEL01 in the frontal cortex. While this finding is intriguing, further genomic analysis studies are required to validate this. In order to assess this clinicians may consider assessing these polymorphisms via a blood test, and can consider measuring the plasmatic levels of PUFAs and fatty acid composition in red blood cells (Fischer et al., 2014).

In respect to other disease groups, the results on the effectiveness of omega 3 are inconclusive. A recent review on the efficacy of omega 3 in treatment of specific mental disorders or clusters of psychiatric symptoms concluded that an overall consensus about their efficacy is still lacking, and findings from studies and reviews are too divergent to draw any conclusion (Bozzatello et al., 2016). However, the main evidence for the effectiveness of omega-3 PUFAs has been obtained in the treatment of depressive symptoms in unipolar and bipolar depression (Bozzatello et al., 2016). Some evidence support the use of omega-3 fatty acids in the treatment of conditions characterized by a high level of impulsivity and aggression, in borderline personality disorders while small-to-modest effects have been found in patients with attention deficit hyperactivity disorder. In schizophrenia, current data are not conclusive. For autism spectrum disorders, anxiety disorders, obsessive-compulsive disorder, eating disorders and substance use disorder, the data are too scarce to draw any conclusion (Bozzatello et al., 2016). There are no conclusive evidence for the efficacy of omega-3 PUFAs supplements in the treatment of refractory epilepsy (Sarmiento et al., 2016) and in the treatment of Alzheimer's disease and in other types of dementia (Burckhardt et al., 2016). Also in cardiovascular diseases the findings are inconclusive (Maehre et al., 2015), however, the partial replacement of saturated fatty acids with unsaturated fatty acids improves the blood lipid and lipoprotein profile and reduces the risk of coronary heart disease (Zock et al., 2016). Moreover, a recent study demonstrates that EPA and DHA are individually effective in diminishing infarct size in experimental model while their combination is not (Madingou et al., 2016).

4.2. Future perspectives

Recently Marriott et al., (2016) presented methods and design of a new study (BRAVO STUDY): a double blind, placebo-controlled trial of omega-3 fatty acid supplementation among veterans and non-veterans at risk of suicide. This study seeks to determine if dietary supplementation with n-3 PUFAs reduces the risk for suicide, suicidal ideations and symptoms associated with suicidal behaviors. A sub-analysis of the study will be performed with functional magnetic resonance imaging (fMRI) to evaluate the neuropsychological and neurophysiological effects of n-3 PUFAs (Marriott et al., 2016).

Another new protocol has been published by Cockayne et al., (2015) for a randomized controlled trial of omega-3 fatty acids and sertraline in an older age cohort at risk for depression. The subjects are being studied with structural neuroimaging to investigate if brain changes are correlated with treatment effects on depressive symptoms. Furthermore, proton spectroscopy techniques are involved to capture brain-imaging markers of the biological effects of the interventions. The primary endpoint will be an absence of relevant depression scores at 12 months between the omega-3 fatty acid and sertraline interventions and the placebo condition.

The outcomes of these works will offer major scientific advances regarding the effects, the neurobiological action and the role in suicide prevention of these agents.

4.3. Our point of view

Our conceptualization of suicide is that suicidal individuals are experiencing unbearable psychological pain, what Shneidman called psychache and that suicide may be, at least in part, an attempt to escape from this suffering. Shneidman (1993a,b) focused on the mentalistic aspects of suicide and suggested that the study of suicidal acts should concentrate on the phenomenology of suicide. Pompili (2010) reported that psychache can be clearly distinguished from depression or other psychiatric disorders because of the uniqueness of suffering perceived by the subject and because of the fact that the subject cannot stand it. The individual cannot see a way out and believes that ending life is a solution. According to Shneidman (1996), suicide risk is associated with constriction or narrowing the range of options usually available to an individual. Shneidman, 1976 reported "The spark that ignites this potentially explosives mixture is the idea that one can put stop to the pain. The idea of cessation provides the solution for the desperate person". Nowadays, suicidologists (Pompili, 2010, 2015) believe that a psychiatric disorder alone is, therefore, not sufficient for precipitating suicide. There must be the suicidality dimension that carries some variant of negative emotions. We now know that psychological pain shares the same neuroanatomical pathways of somatic pain but objectivation of such pain is still problematic (Pompili, 2015), an issue which also applies to the relationship between fatty acids, mental pain and suicide risk. With the rising inside psychiatry of awareness as related with grief as opposed to depression, future research will be able to provide better insight into the phenomenology of suicide and its relationship with biochemistry of central nervous system.

4.4. Limitations

Some shortcomings should be taken into account when analyzing the main findings of the present review. First, the studies reviewed were not homogeneous (some studies have been conducted on healthy individuals, others on subjects with mental illness without adequate control groups, heterogeneous samples were included in most of the selected studies considering mixed patients in various stages of their disorder. It was also difficult to quantify the intake of fish, and interference with medications. In addition, some studies have been conducted as post-mortem reports, and the detection of fatty acid levels was performed on specific brain areas, which are not always generalizable. A meta-analysis was not carried out as available data did not permit us to use such an approach. Different measures and outcomes are reported by the studies that evaluated participants via differing study lengths and methodologies. Some included small sample size, and several methodological problems that affected the main findings and made difficult their generalization. Moreover, some studies analyzed only few variables related to the main topic. Despite that, most of the selected studies were focused on retrospective data, and specific risk factors including gender, age, marital status, and employment status, could be collected reliably, and thus the study design is usually not affected by recall bias. However, clinical variables may be not easily measured to be reliable in retrospective designs. Furthermore, some studies selected only inpatients, analyzed only few variables about the main topics, and did not adequately consider a control group. Finally, a search was not conducted of unpublished data.

4.5. Conclusions

In conclusion, as detailed above, previous research has suggested that low fish consumption is a risk factor, but not the only determinant for suicide mortality several studies found an association between lower levels of fatty acid and suicide; however most studies did not find this association, revealing that the levels of fatty acid in suicidal patients is not statistically significant compared to non-depressed controls. Although several of the reviewed studies demonstrated an association between lower levels of omega-3 fatty acid and suicide, this association is only tentative as the current data is mixed.

Alteration of ratio of PUFAs however may be a potentially important risk factor to examine when assessing suicide risk, with plasma levels of PUFAs potentially providing additional clinical data in the evaluation of patients who are engaging in suicidal behavior. Abnormal levels of PUFAs can induce changes in the epigenome, and these events are associated with suicide. Increasing the intake of fatty acids to address the deficiency in diet combined with medication may be an adjunctive suicide prevention strategy, however currently the data does not support PUFA consumption as a preventative for suicide risk.

Uncited references

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